

REMARKS/ARGUMENTS

Claims 1-28 are pending in the captioned application. Applicants hereby cancel the non-elected claims 18-28 and introduce new claims 29-32. Claim 1 has also been amended. Applicants respectfully request reconsideration in view of the following arguments.

Applicants have amended claim 1 to specify that the dynamic binding capacity in one of the steps is increased by at least 1.5 times compared to a corresponding conventional step without addition of non-ionic polyether. See page 12, line 3 of the published PCT application PCT/SE2005/000467, where a DBC increase of 1.5 times is described for the affinity step. The DBC in the ion-exchange step is increased by a larger amount, i.e., 4-6 times (page 11, line 22 of the published PCT application). Thus the amendment is fairly based on the specification and does not introduce new matter.

Applicants have also added new claims 2-32. Support for claim 29 and 30 can be found in the examples, as well as on page 13, line 5. Support for claim 31 and 32 can be found in the examples, as well as on page 11, line 27 and page 12, line 5. Thus the amendment is fairly based on the specification and does not introduce new matter.

Claims 1-3 and 5-17 stand rejected under 35 U.S.C. §103(a) as being obvious over Shadle et al. (5429746) in view of Feng et al. (Biotech Technique 1998 Vol. 12, page 289-293). Applicants respectfully disagree.

Applicants first submit that the claim rejection appears to have been made under 35 U.S.C. §103(a), as shown by the section title of the office action (page 2), not 35 U.S.C. §102(b) as stated on the first line of page 3. A telephone message was left for the Examiner but did not resolve this issue prior to the filing date of this response.

Applicants submit that as discussed previously, Shadle et al. describes a multistep antibody purification process with protein A affinity chromatography followed by cation exchange chromatography and hydrophobic interaction chromatography. However, as admitted by both Applicants and the Examiner, Shadle et al. does not disclose using non-ionic polyethylene glycol for the isolation and purification of the target proteins. Shadle et al. does not indicate any need to improve capacity, recovery or purification factor.

Feng et al. describes anion exchange chromatography purification of r-TNF in the presence of 0-10% PEG (a nonionic polyether) of molecular weight 200, 400 and 4000. The advantage of having PEG present is said to protect protein activity, improve recovery and purification factor. It is mentioned that at high concentrations, particularly of the higher Mw (Mw 600 and 4000) PEG, the recovery and purification factor is less than that without the addition of PEG (compare Figures 2, 3 and 4, also see p290, right column). It is also mentioned that high concentrations, particularly of the high Mw (Mw 4000) PEG, can have negative effects on the chromatography beads and give high viscosities (see paragraph bridging pages 290-291). At less than 1% PEG no negative effects were found.

Applicants submit that Feng et al. does not mention multistep purification processes. Furthermore, Feng et al. gives no hint that PEG is useful in processes with more than one chromatography step. Still further, Feng et al. would not achieve high DBC. This is related to their range of PEG concentrations and molecular weights. They add PEG 200 at 0-10%, PEG 600 at 0-7% and PEG 4000 at 0-3%. For PEG 600 and 4000 they observe adverse effects on TNF recovery and purification at concentrations above 1%. Overall, their recommendation is not to exceed 1% PEG concentration (p. 291, 2nd col. 1st paragraph).

On the other hand, achieving enhanced dynamic binding capacity is the primary target of the current invention. Figure 5 in the application shows that to get a significant DBC increase in ion exchange, the concentration of PEG 10 000 should be above 2%. Figure 8 shows that over 4% PEG 10 000 is needed to get significant DBC increase on protein A media. It is to be expected that the amounts of lower Mw PEG needed to get these effects are even higher, as the invention is dealing with partitioning phenomena.

Applicants submit that the Examiner is using impermissible hindsight in combining the references. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 873 F.2d 1071, 1075 (Fed. Cir. 1988). While KSR eliminated an absolute requirement for motivation, a claim "composed of several elements is not provided obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The relevant

question is “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *Id.* Applicants submit that Feng et al. relates to anion exchange chromatography of r-TNF, and tries to improve on the poor step recovery of TNF (65%). In comparison, the primary subject of Shadle et al. is HIC purification of IgG and the integration of HIC in processes for IgG, and Shadle et al. already achieves 86% cumulative recovery in a three step process (Table 3) with 100% step recovery in the ion exchange step (Table 3). The present invention relates to increasing the DBC of the chromatography steps in a multistep chromatography process. Applicants submit that there is no motivation to combine the references unless hindsight is used.

Applicants respectfully submit that claims 1-3 and 5-17, as well as the new claims 29-32 are not obvious over Shadle et al. in view of Feng et al.

Claim 4 stand rejected under 35 U.S.C. §103(a) over Shadle et al. in view of Feng et al. and further in view of Bander et al. (US 20040120958). Applicants respectfully disagree. Applicants submit that as discussed above, the combination of Shadle et al. and Feng et al. is improper and claim 1 is patentable. Therefore claim 4 which depends on claim 1 should also be patentable.

Applicants respectfully assert that the claims are in allowable form and earnestly solicit the allowance of the claims 1-17 and 29-32.

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Early and favorable consideration is respectfully requested.

Respectfully submitted,

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